



DEPARTMENT OF VETERANS AFFAIRS

8320-1

Determinations Concerning Illnesses Discussed in National Academy of

Sciences Report: Veterans and Agent Orange: Update 2010

ACTION: Notice.

SUMMARY: As required by law, the Department of Veterans Affairs (VA) hereby gives notice that the Secretary of Veterans Affairs, under the authority granted by the Agent Orange Act of 1991, codified at 38 U.S.C. 1116, has determined that there is no basis to establish a presumption of service connection at this time, based on exposure to herbicide agents, including the substance commonly known as Agent Orange, for several health effects discussed in the September 29, 2011, National Academy of Sciences (NAS) report titled: Veterans and Agent Orange: Update 2010 (hereinafter, "Update 2010"). This determination does not in any way preclude VA from granting service connection for any disease, including those specifically discussed in this notice, nor does it change any existing rights or procedures. In a separate rulemaking, VA will propose to expand the current presumption for peripheral neuropathy.

FOR FURTHER INFORMATION CONTACT: Tom Kniffen, Chief, Regulations Staff (211D), Compensation and Pension Service, Veterans Benefits Administration, Department of Veterans Affairs, 810 Vermont Avenue, NW, Washington, DC 20420, telephone (202) 461-9700. (This is not a toll-free number.)

## SUPPLEMENTARY INFORMATION:

### I. Statutory Requirements

The Agent Orange Act of 1991, Public Law 102-4 (codified in part at 38 U.S.C. 1116), directed the Secretary to seek to enter into an agreement with the National Academy of Sciences (NAS) to conduct a comprehensive review of scientific and medical literature on potential health effects of exposure to Agent Orange. Congress mandated that NAS determine, to the extent possible: (1) whether there is a statistical association between suspect diseases and herbicide exposure, taking into account the strength of the scientific evidence and the appropriateness of the scientific methodology used to detect the association; (2) the increased risk of disease among individuals exposed to the herbicides during service in the Republic of Vietnam during the Vietnam era; and (3) whether a plausible biological mechanism or other evidence of a causal relationship exists between exposure to herbicides and suspect disease.

Section 2 of Public Law 102-4, codified in pertinent part at 38 U.S.C. 1116(b) and (c), provides that whenever the Secretary determines, based on sound medical and scientific evidence, that a positive association (i.e., the credible evidence for the association is equal to or outweighs the credible evidence against the association) exists between exposure of humans to an herbicide agent (i.e., a chemical in an herbicide used in support of the United States and allied military operations in the Republic of Vietnam during the Vietnam era) and a disease, the Secretary will publish regulations establishing presumptive service connection for that disease. If the Secretary determines that

a presumption of service connection is not warranted, he is to publish a notice of that determination, including an explanation of the scientific basis for that determination.

Although 38 U.S.C. 1116 does not define "credible," it does instruct the Secretary to "take into consideration whether the results [of any study] are statistically significant, are capable of replication, and withstand peer review." The Secretary reviews studies that report a positive relative risk and studies that report a negative relative risk of a particular health outcome. He then determines whether the weight of evidence supports a finding that there is or is not a positive association between herbicide exposure and the subsequent health outcome. The Secretary does this by taking into account the statistical significance, capability of replication, and whether that study will withstand peer review. Because of differences in statistical significance, confidence levels, control for confounding factors, bias, and other pertinent characteristics, some studies are more credible than others. The Secretary gives weight to more credible studies in evaluating the overall evidence concerning specific health outcomes.

## II. Prior NAS Reports

NAS has issued nine previous biennial reports under the Agent Orange Act. Based on those reports and the requirements of the Agent Orange Act, VA has established presumptions of service connection for 14 categories of disease, which are listed at 38 CFR 3.307(e). Additionally, following each prior NAS report, VA has published a notice explaining the Secretary's determination that

presumptions of service connection are not warranted for several diseases discussed in those reports. Those notices are published at: 59 FR 341 (Jan. 4, 1994), 61 FR 41442 (Aug. 8, 1996), 64 FR 59232 (Nov. 2, 1999), 67 FR 42600 (Jun. 4, 2002), 68 FR 27630 (May 30, 2003), 72 FR 32395 (May 20, 2007), 75 FR 32540 (Jun. 8, 2010), and 75 FR 81332 (Dec. 27, 2010). The Secretary's determination that there is not a positive association between herbicide exposure and the diseases addressed in this notice is based upon the prior NAS reports, as discussed in VA's prior Federal Register notices, and upon the additional information and analysis in Update 2010, as discussed below.

### III. Veterans and Agent Orange: Update 2010

On September 29, 2011, NAS publicly released Veterans and Agent Orange: Update 2010, which describes the relevant scientific and medical evidence identified subsequent to the last prior NAS review, Veterans and Agent Orange: Update 2008 (hereinafter, "Update 2008"). NAS reviewed, evaluated, and summarized scientific and medical literature addressing several conditions and the health status of veterans.

Consistent with its prior reviews, NAS concentrated its review on epidemiologic studies to fulfill its charge of assessing whether specific human health effects are associated with exposure to at least one of the herbicides utilized or to a chemical component of herbicides, such as TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin; referred to as TCDD to represent a single – and the most toxic – congener of the tetrachlorodibenzo-*p*-dioxins, also commonly

referred to as dioxin). . NAS also considered controlled laboratory investigations that provided information on whether the association between the chemicals of interest and a given effect is biologically plausible.

In Update 2010, NAS endeavored to emphasize and clarify the relationship among the succession of publications that have provided ever increasing insight into the health responses of particular exposed populations that have been studied for many years. The information that the present Committee reviewed was identified through a comprehensive search of relevant databases, including databases covering biologic, medical, toxicologic, chemical, historical, and regulatory information. NAS conducted a comprehensive search of all medical and scientific studies on health effects of herbicides used in the Vietnam War, including more than 6,600 potentially relevant studies, of which 1,300 were carefully reviewed, and about 65 ultimately contributed new information. Relevant animal studies, as with previous biennial "Agent Orange Updates," were also reviewed to determine biological plausibility and possible mechanisms of action.

The epidemiologic information evaluated in Update 2010 was integrated with that previously assembled included veterans studies, occupational studies, and environmental studies. NAS reviewed three studies of veterans published since Update 2008. One study on Army Chemical Corps personnel produced findings related to causes of mortality, while another study on Australian veterans evaluated the prevalence of a multitude of self-reported health outcomes, including cancers, circulatory diseases, respiratory diseases, diabetes, and

digestive disorders. A third study examined the progression of prostate cancer in a case-control study of veterans with previous Agent Orange exposure.

Since Update 2008, several occupational studies have been published. For example, recent reports from the Agricultural Health Study examined the incidence of pancreatic cancer, hearing loss, melanoma, thyroid disease, adult onset asthma, myocardial infarction, and rhinitis in private pesticide applicators (farmers), their spouses, and commercial pesticide applicators. Additionally, circulatory diseases and neurologic outcomes were studied in a 40-year follow-up of Czech production workers who were exposed to TCDD during the production of 2,4,5-T.

Since Update 2008, numerous studies from environmental exposures to chemicals of interest have been published. Reproductive outcomes, including birth weight, birth defects, childhood cancer, neonatal thyroid function, and development of childhood obesity were studied in offspring of mothers exposed to TCDD and other chemicals with dioxin-like biologic activity from incinerator emissions in France, the industrial accident at Seveso, Italy, and dietary intake in Taiwan, Italy, Belgium, the Netherlands, and Japan. Cancer outcomes were evaluated in follow-up studies of residents of Seveso, Italy, and farmers and pesticide applicators/users in Canada and the US. Diabetes and conditions associated with metabolic syndrome were assessed in Great Lakes sport-fish consumers, Taiwanese residents near a pentachlorophenol factory, Finnish fisherman, Japanese men and women, and the general US population via the National Health and Nutrition Examination Survey. New case-control studies

examined environmental exposures to the chemicals of interest and endometriosis and Parkinson's disease.

As in its prior reports, NAS placed each health outcome it reviewed in one of four categories based on the strength of the evidence of association between herbicide exposure and the health outcome. The four categories are: Sufficient Evidence of Association; Limited or Suggestive Evidence of Association; Inadequate or Insufficient Evidence to Determine Whether an Association Exists; and Limited or Suggestive Evidence of No Association. VA has established presumptions of service connection for all diseases NAS placed in the first category and for most of the diseases NAS placed in the second category. This notice explains the basis for VA's determination that presumptions of service connection are not warranted for the remaining diseases discussed in Update 2010.

#### Limited or Suggestive Evidence of an Association

NAS has defined this category of association to mean that the "evidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence."

#### Hypertension

NAS placed hypertension in the "Limited or Suggestive Evidence of Association" category. Hypertension affects more than 70 million adult

Americans and is a major risk factor for coronary artery disease, myocardial infarction, stroke, and heart and renal failure. A recent study of the Framingham cohort (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2004) showed that in both 55 and 65-year-old participants, the cumulative lifetime risk for the development of hypertension (at or above 140/90 mm Hg, regardless of treatment) was 90%. The lifetime risk statistic is the probability that an individual will develop a disease over a lifetime. Major risk factors are well established and include tobacco use, diet, physical inactivity, obesity, diabetes mellitus, alcohol, and heredity.

In its reports prior to 2006, NAS placed hypertension in the “Inadequate or Insufficient Evidence” category. In Veterans and Agent Orange: Update 2006 (hereinafter, “Update 2006”) and Update 2008, NAS elevated hypertension to the “Limited or Suggestive Evidence” category, but could not clearly distinguish the possibility of a small increased risk for hypertension due to herbicide exposure from more prevalent scientifically established risk factors in evaluating the risk to individual veterans. NAS noted the limitations of the studies regarding hypertension. In the Federal Register of June 8, 2010, and December 27, 2010, VA explained why the studies reviewed in Update 2006 and Update 2008 did not, in VA’s view, warrant a presumption of service connection for hypertension in veterans exposed to herbicides in service. 75 FR 32540 (Jun. 8, 2010); 75 FR 81332 (Dec. 27, 2010).



In Update 2010, NAS reviewed and weighed previous literature from its prior reports and five new epidemiology studies published since Update 2008. To varying degrees, a limitation of all the new studies was an inability to adjust for known risk factors for hypertension. A study of Army Chemical Corps veterans found a statistically nonsignificant increase in hypertension mortality and was unreliable due to the small sample size. Another study found a 13% increase in self-reported hypertension among Australian Vietnam veterans. However, NAS found that report unreliable because it was based solely on self-reports, it was not based on exposure information, and did not account for confounding risk factors. NAS further noted that a study of Czech workers exposed to herbicides was unreliable due to the small sample size, lack of a well-defined comparison population, and lack of comparison data between the exposed and non-exposed populations. Another study examined the relationship between metabolic syndrome and the body burden of dioxin and related compounds in the Japanese general population. This study found that subjects in the highest quartile of serum levels of dioxin-like polychlorinated biphenyls (PCBs) from environmental exposure had a significant increased prevalence of hypertension. The cross-sectional design of this study (in which subjects are assessed at a single time in their lives) limits its ability to quantify risk, establish a causal relationship, and rule out confounding factors. Important risk factors that could account for the increased incidence of hypertension, such as body weight, sodium intake, and dietary exposure, were not adjusted for. The fifth new study examined newly diagnosed hypertension and its relationship to serum levels of

persistent organic pollutants from the National Health and Nutrition Examination Survey (NHANES) 1999-2002. This study was also cross-sectional in design, limiting its ability to quantify risk, establish a causal relationship, and rule out confounding factors. This study adjusted for only some confounders and used the lowest serum measures of pollutants as the referent population. No association between dioxin-like PCBs and hypertension was found in men even at the highest serum levels. In addition, there were no indications of a positive trend towards an association. Women had a significant association for some persistent organic pollutants but not dioxin-like PCBs. Significant variation is seen across dioxin-like compounds in these studies. Researchers have grouped dioxin-like compounds for their cancer induction effects, but these variations in hypertension results bring uncertainty to this grouping for non-cancer effects.

VA has reviewed this additional information in relation to the information in prior NAS reports analyzing studies concerning hypertension. Based on this review, the Secretary has determined that the available evidence presented in Update 2010 is not sufficient to establish a new presumption of service connection for hypertension in veterans exposed to herbicides. As noted in VA's evaluation of prior NAS reports, 75 FR 32540 (Jun. 8, 2010), the evidence overall includes a wide variety of results. While some veteran studies have reported increased incidence of hypertension, others have found no increase. Similarly, numerous environmental and occupational studies have found no significant increased risk of hypertension. The consistently negative findings of occupational studies are of interest because, at least in studies of chemical-

production workers, the magnitude and duration of exposures in occupational studies generally would be greater than in Vietnam veteran studies. Further, as noted above, several of the studies that provide evidence of an increased risk are limited by the failure to control for significant confounders or by other methodological concerns. Accordingly, the Secretary has determined that the available evidence does not at this time establish a positive association between herbicide exposure and hypertension that would warrant a presumption of service connection.

#### Inadequate or Insufficient Evidence to Determine an Association

NAS has defined this category of association to mean that available epidemiologic studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding factors, have inadequate exposure assessment, or fail to address latency.

Consistent with its findings in Update 2008, NAS in Update 2010, found inadequate or insufficient evidence to determine whether an association exists between herbicide exposure and the following conditions: 1) cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), and nasal cavity (including ears and sinuses); 2) cancers of the pleura, mediastinum, and other unspecified sites within the respiratory system and intrathoracic organs; 3) cancers of the digestive organs (esophageal cancer; stomach cancer; colorectal cancer (including small intestine and anus), hepatobiliary cancers

(liver, gallbladder, and bile ducts), and pancreatic cancer); 4) bone and joint cancer; 5) melanoma; 6) non-melanoma skin cancer (basal cell and squamous cell); 7) breast cancer; 8) cancers of the reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate); 9) urinary bladder cancer; 10) renal cancer (kidney and renal pelvis); 11) cancers of the brain and nervous system (including eye); 12) endocrine cancers (including thyroid and thymus); 13) leukemia (other than all chronic B-cell leukemias including chronic lymphocytic leukemia and hairy cell leukemia); 14) cancers at other and unspecified sites (other than those as to which the Secretary has already established a presumption); 15) reproductive effects (including infertility; spontaneous abortion other than after paternal exposure to TCDD; and -- in offspring of exposed people -- neonatal death, infant death, stillborn, low birth weight, birth defects [other than spina bifida], and childhood cancer [including acute myeloid leukemia]); 16) neurobehavioral disorders (cognitive and neuropsychiatric); 17) neurodegenerative diseases (including amyotrophic lateral sclerosis (ALS) but excluding Parkinson's disease); 18) chronic peripheral nervous system disorders (other than early-onset peripheral neuropathy); 19) respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung); 20) gastrointestinal, metabolic, and digestive disorders (including changes in liver enzymes, lipid abnormalities, and ulcers); 21) immune system disorders (immune suppression, allergy, and autoimmunity); 23) circulatory disorders (other than hypertension and ischemic heart disease); 24) endometriosis; and 25) effects on thyroid homeostasis. Further, NAS found inadequate or insufficient evidence to

determine whether an association exists between herbicide exposure and the following three conditions, which were evaluated for the first time in Update 2010:

1) hearing loss; 2) eye problems; and 3) bone conditions.

With respect to the 25 categories of disease considered in its prior reports, NAS found that the studies published since Update 2008 generally did not contain statistically significant findings or other significant evidence of association between herbicide exposures and those health outcomes, with a few exceptions discussed below.

NAS noted that a follow-up study of residents environmentally exposed to dioxin following an accidental release in Seveso, Italy, found a “barely significant” increased risk of biliary cancer in residents of the moderately-exposed zone, but that no excess was found in the high or low exposure zones. Additionally, two new occupational studies found no statistically significant increased risk of hepatobiliary cancers in exposed workers. NAS concluded that the isolated finding among the moderately-exposed group in the Seveso study did not establish a consistent pattern of risk and that the overall evidence was insufficient to link the chemicals of interest with hepatobiliary cancers.

NAS noted that the Seveso study also found a statistically significant increase in the incidence of breast cancer among female residents of the high exposure zone 10-14 years after the accident. However, NAS also noted that a recent occupational study and a 2008 study of female Vietnam veterans did not support an increased risk of breast cancer mortality in exposed populations.

Overall, NAS concluded that the evidence remains inadequate or insufficient to determine whether an association exists.

NAS noted that a study of herbicide production workers reported an “infinitely large” hazard ratio for risk of renal cancer based on eight deaths in the exposed group and none in the control group, but NAS also stated that the moderate size of the cohort limited the study’s ability to detect an increase in this relatively rare cancer. Further, the findings of that study were not supported by several other new occupational and environmental studies, which found no increased risk of renal cancer or found moderate but not statistically significant increases. Accordingly, NAS found the evidence overall inadequate or insufficient to determine whether an association exists.

NAS noted that the Seveso follow-up study reported a statistically significant increased incidence of myeloid leukemia in the moderately exposed group but not in the group with the highest exposure. NAS noted that the significance of this finding was limited by concerns about possible misclassification of that type of leukemia and the erratic correlation between intensity of exposure and degree of risk. Further, that finding was not supported by other new occupational and Vietnam Veteran studies, which generally found no increased risk of leukemia in exposed populations.

NAS noted that two new studies reported statistically significant evidence of association between herbicide exposure and chronic obstructive pulmonary disease (COPD). A study of Army Chemical Corps veterans reported a statistically significant excess mortality from COPD. However, NAS found the

significance of that finding to be significantly constrained by the inability to fully control for cigarette smoking, the major risk factor for COPD. NAS noted that prior studies of American Vietnam veterans did not find evidence of increased mortality due to noncancerous respiratory conditions. NAS noted that concerns regarding misclassification of COPD on death certificates and misdiagnosis of COPD further limit the conclusion that can be drawn from such mortality data. The other new study found a statistically significant increase in self-reported incidence of emphysema and bronchitis, which are conditions consistent with COPD, among Australian Vietnam veterans. NAS noted that this finding was limited by recall bias and other methodological considerations and expressed general skepticism about the significance of this study's findings due to its low response rate and the study's nearly uniform findings of statistically increased prevalence for nearly 50 health conditions. NAS further noted that prior studies of the full cohort of male Australian Vietnam veterans showed no suggestion of increased mortality from COPD or other noncancerous respiratory conditions and that a number of occupational studies failed to detect an increased risk of COPD or other noncancerous respiratory conditions. Accordingly, NAS found the evidence overall inadequate or insufficient to determine whether an association exists between herbicide exposure and COPD or other noncancerous respiratory conditions.

With respect to immune system disorders, NAS noted that the only potentially relevant new study was the above-referenced Australian veteran study, which found that several conditions in which immune function may play a

role – including infectious and parasitic diseases, respiratory disorders, and skin disorders – were significantly more prevalent in Australian Vietnam veterans, based on self-reports, than among the general population. For the same reasons discussed above, NAS found the reliance that could be placed on that report to be significantly limited by numerous methodological concerns. Accordingly, NAS found that there was inadequate or insufficient evidence to determine whether an association exists between herbicide exposure and immune system disorders.

In notices following prior NAS reports, cited in section II above, VA has explained the basis for the Secretary’s determination that a positive association does not exist between herbicide exposure and the health conditions identified in Update 2010 in the “inadequate or insufficient evidence” category (other than the three new conditions discussed below). For the reasons explained above, VA has determined that the additional studies discussed in Update 2010 do not change the Secretary’s determination that a positive association does not currently exist between herbicide exposure and those health conditions.

In Update 2010, NAS for the first time evaluated available studies regarding the possible association of hearing loss with herbicide exposure. The NAS found two potentially relevant studies, both of which were based on self-reports of hearing loss. In the study of Australian Vietnam veterans, discussed above, Vietnam veterans had an increased risk of diseases of the ear, tinnitus, or deafness, compared to the general population. As previously discussed, NAS had serious concerns that the results of this study were compromised due to recall bias and several other methodological concerns. The second study found



an increased risk of hearing loss among licensed pesticide applicators overall, although analyses by pesticide class did not show strong associations with hearing loss. Moreover, although applicators who reported insecticide use had a higher rate of self-reported hearing loss compared to those with no reported insecticide use, applicators who reported more than 651 days of lifetime herbicide use had no increase in self-reported hearing loss compared to non-exposed persons. Accordingly, the study does not provide evidence of an association between herbicide exposure and hearing loss. NAS further noted that both studies were limited by the lack of clinical confirmation of hearing loss, among other factors. Accordingly, NAS concluded that the evidence was inadequate or insufficient to determine whether an association exists between herbicide exposure and hearing loss.

Update 2010 also addressed eye problems for the first time. The sole study potentially relevant to eye conditions was the previously described Australian Veteran study, which found increases in self-reported incidence of cataracts, presbyopia, color blindness, and other diseases of the eye among Australian Vietnam veterans compared to the general population. Again, NAS noted that it had serious concerns that the results of this study were compromised by several methodological issues. Accordingly, the NAS did not regard this report as providing evidence that could indicate whether an association exists between herbicide exposure and eye problems.

Update 2010 also addressed bone disorders for the first time. The sole potentially relevant study identified by NAS was a study of forearm bone mass

density among individuals who may have had exposure to dioxin like polychlorinated biphenyls from fish consumption. The study found that one of the PCBs under examination had a positive association with bone mass density in women but not in men and that, when low bone mass density was treated as a variable, a positive association was observed in men, but not in women. NAS found that this report provided a relatively small amount of information, was limited to the effect on one dioxin-like PCB, and indicated no consistent pattern on which to determine whether herbicide exposure is associated with bone disorders.

Based on the analysis in Update 2010, the Secretary has determined that the available studies generally do not provide credible evidence of an association between exposure to an herbicide agent and an increased risk of hearing loss, eye problems, or bone conditions. The Secretary therefore finds that a positive association does not currently exist between herbicide exposure and those conditions and that no presumption of service connection is warranted for those conditions at this time.

#### Limited or Suggestive Evidence of No Association

NAS has previously concluded that there is limited or suggestive evidence of no association between paternal herbicide exposure and spontaneous abortion. In Update 2010, NAS identified no new studies relevant to that health outcome. Accordingly, the Secretary has determined that there is no positive association between paternal herbicide exposure and spontaneous abortion.

Detailed information on NAS' findings may be found at <http://www.iom.edu/Reports/2011/Veterans-and-Agent-Orange-Update-2010.aspx>. After selecting the link titled: "Read Report Online for Free," report findings, organized by category, may be found under the heading, "Table of Contents."

Conclusion:

After careful review of the findings of the 2010 NAS report, Veterans and Agent Orange: Update 2010, the Secretary has determined that based on the scientific evidence presented in this report and prior NAS reports, no new presumptions of service connection are warranted at this time for any of the conditions discussed in this notice.

Signing Authority

The Secretary of Veterans Affairs, or designee, approved this document and authorized the undersigned to sign and submit the document to the Office of the Federal Register for publication electronically as an official document of the Department of Veterans Affairs. John R. Gingrich, Chief of Staff, Department of Veterans Affairs, approved this document on June 6, 2012, for publication.

Dated: August 7, 2012

---

Robert C. McFetridge,  
Director, Regulation Policy and Management,  
Office of the General Counsel  
Department of Veterans Affairs

[FR Doc. 2012-19635 Filed 08/09/2012 at 8:45 am; Publication Date: 08/10/2012]